



April 26, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

**Re: Docket 05D-0004 – Draft Guidance for Industry on Nonclinical Safety
Evaluation of Drug Combinations**

Merck & Co., Inc. is a leading worldwide human health product company. Merck's corporate strategy — to discover new medicines through breakthrough research — encourages us to spend nearly \$3 billion annually on worldwide Research and Development (R&D). Through a combination of the best science and state-of-the-art medicine, Merck's R&D pipeline has produced many of the important pharmaceutical and biological products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R&D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. In the course of developing products to treat and prevent a variety of diseases, Merck scientists regularly address issues affected by the draft guidance (hereafter referred to as the Guidance). Therefore, we are well qualified to comment on this guidance.

In general, we commend the FDA on its effort to provide further guidance for the specific therapeutic class of oncology drugs. However, we have identified areas that the FDA should consider when finalizing this draft guidance. Specifically, we believe that the FDA's final guidance should include details of how to determine the appropriate dose ratio of the combinations to be used for the bridging safety/toxicity studies. MRL proposes that for initial combination studies, when necessary, 3 dose groups should be studied as follows: 1) a ratio of 1 to 1 for each drug in the combination; 2) high dose of one combination with low dose of the other; and 3) a reverse of the high dose and low dose combination of each drug. This study design would explore elicitation of potential toxicity across a wide range of dose ratios and provide the best support for clinical exploration of a safe and effective combination dose ratio.

Docket 05D-0004 – Draft Guidance for Industry on Nonclinical Safety Evaluation of Drug Combinations-page 2

We also recommend that for combination drug products involving established drug products (i.e., marketed drug products), the initial combination studies described above should be conducted in only 1 animal species (rodent). Additionally, if the combination drug product involves one or more new molecular entities (NMEs), the studies should be completed in 2 species (1 rodent and 1 non-rodent).

Further, MRL recommends that for combination drug products involving marketed drugs with extensive clinical experience, well defined PK and PD profiles, and monitorable adverse effects, the FDA should not require clinical drug safety pharmacology studies to determine the PK/PD of the combination product to establish the appropriate ratio to be used for bridging studies.

In addition to the general comments provided above, we have included additional comments that relate to specific sections of the guidance document.

Specific Comments

Lines 125 and 126

“FDA recommends that combination studies include an assessment of several dose levels of the combinations and a high dose of each drug alone.”

MRL Recommendation: Based on the fact that each Marketed Drug (MD) product will have undergone previous extensive safety testing to support their registration as monotherapies, it is not clear why high doses of individual drugs alone should be included in the study design since, in most cases, NOAEL and LOAEL doses will have been previously determined. Furthermore, the high dose of each drug in the combination studies need not be as high as the toxic doses individually, provided kinetic evaluation has established that one drug does not influence the TK of the other and if the target human doses of the individual drug would be lower than if given individually. Therefore, we recommend that for initial combination studies, when necessary, 3 dose groups should be studied as follows: 1) a ratio of 1 to 1 for each drug in the combination; 2) high dose of one combination with low dose of the other; and 3) a reverse of the high dose and low dose combination of each drug.

Lines 157 – 159

“Generally FDA recommends that sponsors conduct nonclinical toxicity studies before clinical studies are initiated if (1) the drug products have similar target organs of toxicity or pharmacologic activity ...”

MRL Recommendation: The need for nonclinical combination studies prior to clinical studies in the case of two MD's with identified and monitorable toxicity is unclear. This statement is also inconsistent with the flow chart diagram on page 10, line 359-361. The flow chart states toxicity that cannot be monitored is of concern. We suggest modifying the text in lines 158-159 to make the information in this section and figure A consistent,

as follows: “1) the drug products have similar target organ toxicity or pharmacodynamic activity and the toxicity cannot be monitored...”

Lines 174 – 177

“Combination developmental toxicity studies need not be conducted if one of the drug products is already known to have significant risk for developmental toxicity, because that risk will already be included in the product labeling for the combination.”

MRL Recommendation: We believe that significant risk for developmental toxicity should be defined in order to identify the distinctions between serious (teratogenicity) and minor (decreased fetal weight gain) reproductive effects. Pregnancy Category C or D would have different liabilities. The guidance should be worded in such a way that there would be no requirement to conduct an additional developmental toxicity study of the combination product when a severe adverse effect (teratogenic) has been established for one of the drugs.

Lines 205-206

“For combinations, FDA recommends that the drug be at ratios that are relevant to the intended clinical use.”

MRL Recommendation: With regard to 90-day bridging studies, MRL strongly agrees with the Agency that nonclinical bridging studies that test combination products of MDs and New Molecular entities (NMEs) in ratios relevant to the intended clinical use is the best path for these studies. Since the clinically relevant ratios of the combination product will not be known until Phase II, we recommend that the doses for the bridging studies include a wide range of ratios tested in 3 separate dose groups but need not include the final clinical ratio (see General Comments)

Lines 219-221

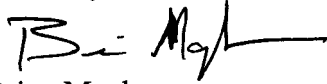
“If there is known significant risk, embryofetal development studies of the NME would not be needed, because of the labeling would not be changed in this regard for the combination.”

MRL Recommendation: MRL requests further clarification from the FDA concerning cases where no developmental toxicity is seen in the initial individual studies of a MD and a NME, and further clarity for circumstances where slight toxicity is seen in either the MD or the NME to be used in combination products. It would also be important to clarify “embryofetal development effect” as this could cover effects ranging from embryonal death (post implantation loss), fetal developmental delay to teratogenicity. It would be advisable to conduct segment II study in 2 species with the NME to evaluate for potential teratogenic effects unless this has been seen with the marketed drug.

**Docket 05D-0004 – Draft Guidance for Industry on Nonclinical Safety
Evaluation of Drug Combinations-page 4**

We welcome the opportunity to work with the FDA on this important initiative. If you have any questions related to the information provided above, please feel free to contact me at (301) 941-1402.

Sincerely,

A handwritten signature in black ink, appearing to read "Brian Mayhew". The signature is fluid and cursive, with a long horizontal stroke at the end.

Brian Mayhew
U.S. Regulatory Policy